REMARKS

Status of the Claims

Pending claims

Claims 1 to 93 are pending.

Claims canceled in the instant amendment

Claims 6, 7, 81, 82 and 88 are canceled. Claims 38 to 43, 51 to 53 and 56 remain withdrawn as drawn to a non-elected species (however, when the elected species is held to be allowable, Applicants request consideration (examination) of the withdrawn additional species). Thus, claims 1 to 5, 8 to 80, 83 to 87 and 89 to 93 will remain pending and under consideration.

Restriction Requirement and Election

In the restriction requirement dated May 14, 2002, the Patent Office alleged that the pending claims of the application were directed to three separate and distinct inventions under 35 U.S.C. §121:

I. Claims 1-7, 11-13, 17-82 and 87, drawn to a method of ligand screening using nucleic acids, classified in class 435, subclass 6.

II. Claims 1-5, 8-80, 83-87, drawn to a method of ligand screening using proteins, classified in class 435, subclass 7.1.

III. Claim 88, drawn to a cell system, classified in class 435, subclass 240.2.

In response to the Restriction Requirement, Applicants elected Group II, claims 1-5, 8-80, 83-87, drawn to a method of ligand screening using proteins.

The Patent Office further alleged that the claims are directed a first set of patentably distinct species as follows:

Species I – *E. coli* ViaA gene, claim 37

Species II – *E. coli* orf1 gene, claim 38

Species III – *E. coli* lepB gene, claim 39

Species IV – *E. coli* ugpB gene, claim 40

Species V – *E. coli* ddiB gene, claim 41

Species VI – *E. coli* secA gene, claim 42

Species VII – *E. coli* fimF gene, claim 43

Species VIII – *E. coli* fimD gene, claim 43

The Patent Office further alleged that the claims are directed a second set of patentably distinct species as follows:

Species 1 – bacterium

Species 2 – gram negative bacterium

Species 3 – *E. coli*

Species 4 – gram positive bacterium

Species 5 – *Staph. aureus*

Species 6 – fungus

Species 7 – yeast

Species 8 – *Archaebacteria*

Species 9 – pathogen (e.g., viruses)

In response, Applicants elected Species I – *E. coli* ViaA gene, claim 37, and Species 1 – bacterium.

When the elected species is held to be allowable, Applicants are entitled to consideration (examination) of additional species; if all species are held to be allowable, a generic claim should be allowed (MPEP §809.02(c); pg 800-50, 8th Edition, August 2001). Applicants respectfully request examination of the withdrawn, additional species, and, when all species are held to be allowable, allowance of a generic claim.

Outstanding Rejections

Claims 1 to 5, 8 to 22, 24, 26 to 30, 32, 34 to 36, 44 to 50, 54, 55, 57, 58, 61, 63 to 71, 75, 77 to 80, 83 to 87 and 89 to 93 stand newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, et al., U.S. Patent No. 6,037,123 (hereinafter "Benton"), in view of Roninson, et al., U.S. Patent No. 5,811,234 (hereinafter "Roninson"), and further in view of Timberlake, U.S. Patent No. 5,821,076 (hereinafter "Timberlake").

Claims 23, 31, 59 and 60 stand newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake and further in view of Gossen, et al., Current Opinion Biotechnology (1994) 5:516-520 (hereinafter "Gossen").

Claims 25, 33 and 62 stand newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake and further in view of Mirabelli, et al., U.S. Patent No. 5,639,595 (hereinafter "Mirabelli").

Claims 72 to 74 stand newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake and further in view of Lam, et al., U.S. Patent No. 5,510,240 (hereinafter "Lam").

Claims 76 stands newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake and further in view of Matsunaga, et al., U.S. Patent No. 4,788,038 (hereinafter "Matsunaga").

Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

Issues under 35 U.S.C. §103(a)

Benton, in view of Roninson, and further in view of Timberlake

Claims 1 to 5, 8 to 22, 24, 26 to 30, 32, 34 to 36, 44 to 50, 54, 55, 57, 58, 61, 63 to 71, 75, 77 to 80, 83 to 87 and 89 to 93 stand newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake.

The Patent Office cites Benton for teaching, inter alia, a method of screening for an antimicrobial agent. The Patent Office states that Benton does not teach a method for identification of microbial proliferation genes by using random fragments.

Roninson is cited to cure this defect in Benton. The Patent Office cites Roninson for teaching, inter alia, a method of screening for genetic suppressor elements which may be targeted at genes essential for growth comprising introducing a randomly fragmented nucleic acid element.

Timberlake is cited for, inter alia, evidencing that essential genes are required for proliferation.

Applicants respectfully aver that Benton is further defective in that Benton does not teach or suggest a method for identification of microbial proliferation genes by a method comprising use of an exogenous nucleic acid that is a random antisense fragment or a random

antisense sequence. In addition to not teaching a method for identification of microbial proliferation genes by using random fragments, Benton does not teach or suggest expressing the microbial proliferation gene in an antisense orientation.

In further contrast to the instant invention, Benton's method comprises identifying essential genes using temperature sensitive mutants (ts mutants), as discussed, inter alia, on column 2, lines 9 to 23, of Benton:

> For the *Staphylococcus aureus* essential genes identified in this invention, the essential nature of the genes was determined by the isolation of growth conditional mutants of *Staphylococcus aureus*, in this case temperature sensitive mutants (ts mutants). Each gene was then identified by isolating recombinant bacteria derived from the growth conditional mutant strains, which would grow under non-permissive conditions but which were not revertants. These recombinant bacteria contained DNA inserts derived from the normal (i.e., wild-type) *S. aureus* chromosome which encoded non-mutant products which replaced the function of the products of the mutated genes. The fact that a clone having such a recombinant insert can complement the mutant gene product under non-permissive conditions implies that the insert contains essentially a complete gene, since it produces functional product.

See also, e.g., column 8, lines 9 to 27 of Benton:

> Also provided is a method of screening for an antibacterial agent by determining whether a test compound is active against one of the genes identified in the first aspect. In a particular embodiment the method is performed by providing a bacterial strain having a mutant form of a gene selected from the group of genes corresponding to SEQ. ID. NOS. 1-105 or a mutant gene homologous to one of those genes. The mutant form of the gene confers a growth conditional phenotype, e.g., a temperature-sensitive phenotype, on the bacterial strain having that mutant form. A comparison bacterial strain having a normal form of the gene is also provided and the two strains of bacteria are separately contacted with a test compound under semi-permissive growth conditions. The growth of the two strains in the presence of the test compound is then compared; a reduction in the growth of the bacterial strain having the mutant form compared to the growth of the bacterial strain having the normal form of the gene indicates that the test compound is active against the particular gene. [emphasis added]

No Suggestion or Motivation to Modify the References

Applicants respectfully aver that because there is no suggestion or motivation in the cited art to modify or supplement the primary reference, Benton, et al., i.e., there is no suggestion or motivation in the cited art to combine Benton with Roninson, and further with

Timberlake, a *prima facie* case of obviousness has not been made, and the rejection under section 103 can be properly withdrawn.

There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998); see also MPEP §2143.01. The level of skill in the art cannot be relied upon to provide the suggestion to combine references [emphasis added]. Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Benton's method involves, inter alia, identifying essential genes by the isolation of growth conditional mutant strains and the complementation in recombinant strains of each of the mutated [growth conditional mutant] genes under non-permissive conditions by expression from artificially-inserted DNA sequences carrying non-mutated (wild type) genes (see, e.g., column 2, lines 38 to 55, of Benton). Benton does not teach or suggest any remaining unsolved problem or any defects or shortcomings with their method for identifying essential genes, as described in USPN 6,037,123. Thus, Benton does not teach or suggest modifying their method for identifying essential genes.

The teachings of the cited art, including the cited Roninson or Timberlake, also do not teach or suggest any problem to be solved or any defects or shortcomings with the method for identifying essential genes as described in USPN 6,037,123. The teachings of Benton and the teaching of the cited art do not teach or suggest a need to modify or supplement the way essential genes are identified in the method described in USPN 6,037,123. Accordingly, there is no explicit teaching, suggestion, or motivation to combine the cited references.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also In re Fine,

837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As discussed above, Applicants have shown that there is no explicit teaching, suggestion, or motivation to combine the cited references. Applicants respectfully aver that there is also no implicit showing teaching, suggestion, or motivation to combine the cited references. Following the test for an implicit showing, there are no combined teachings that teach or suggest a reason to modify the methods of Benton. There are no teachings, suggestions, or motivations that there is any defect or further problem to be solved in Benton. One skilled in the art would not have combined Roninson with Benton without benefit of the teachings of the instant specification. Accordingly, there is no or implicit teaching, suggestion, or motivation to combine the cited references.

Accordingly, because there is no explicit or implicit teaching, suggestion, or motivation to combine the cited references, the combining of Benton with Roninson and/or Timberlake is improper hindsight reconstruction.

Motivation to combine references requires that the combination sought to be made be desirable, not merely feasible. Winner International Royalty Corp v. Wang, 53 USPQ2d 1580, 1587 (Fed Cir. 2000). However, there is no suggestion in the art that it is merely feasible, much less desirable, to use the methods of Roninson to complement, replace or supplement the methods of Benton.

The Patent Office alleges that there is motivation to combine the gene suppressor element (GSE) method of Roninson with the antimicrobial screening of Benton because Benton states "... the invention provides a method of screening for an antibacterial agent by determining the effects of a test compound on the amount or level of activity of a polypeptide gene product of one of the identified essential genes." However, Benton does not teach or suggest any shortcomings or problems with the methods they used to identify essential genes.

It is further alleged that one of skill in the art would have substituted Benton's method for identifying essential genes with the method of Roninson because, inter alia, Roninson states "The invention provides a general method for obtaining effective genetic suppressor elements (GSEs) for cloned genes or viruses, without extensive structure/ function information, and in a simple selection or screening procedure." However, Roninson does not teach or suggest

that Benton's method for identifying essential genes (e.g., by the isolation of growth conditional mutant strains and the complementation in recombinant strains of each of the mutated [growth conditional mutant] genes under non-permissive conditions by expression from artificially-inserted DNA sequences carrying non-mutated (wild type) genes) is defective, problematic or needs supplementing or replacing. Thus, the combining of Benton with Roninson is improper hindsight reconstruction.

The Patent Office cites Timberlake as further motivation to screen for such essential genes because Timberlake demonstrates that essential genes are excellent targets for therapeutic agents. However, Timberlake does not teach or suggest that Benton's method for identifying essential genes (e.g., by the isolation of growth conditional mutant strains and the complementation in recombinant strains of each of the mutated [growth conditional mutant] genes under non-permissive conditions by expression from artificially-inserted DNA sequences carrying non-mutated (wild type) genes) is defective, problematic or needs supplementing or replacing. Thus, the combining of Benton with Timberlake is improper hindsight reconstruction.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). None of the cited references teach or suggest the desirability of the combination. None of the cited references teaches or suggests the desirability of modifying the methods of Benton. The skilled artisan, without the teaching of the specification, would not have been motivated to substitute Roninson's (GSE) method for identifying essential genes with the method of Benton. Thus, the combining of Benton with Timberlake is improper hindsight reconstruction.

Applicants respectfully aver that because there is no suggestion or motivation in the cited art to modify or supplement Benton, there is no suggestion or motivation in Benton that there remains a problem to be solved, and there is no explicit or implicit teaching, suggestion, or motivation to combine the cited references, a *prima facie* case of obviousness has not been made, and the rejection under section 103 citing Benton, in view of Roninson, and further in view of Timberlake, can be properly withdrawn.

Benton, in view of Roninson, and further in view of Timberlake and Gossen

Claims 23, 31, 59 and 60 stand newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake and further in view of Gossen.

However, as discussed above, Applicants respectfully aver that there is no suggestion or motivation in the cited art, including Gossen, to modify or supplement Benton. There is no suggestion or motivation in Benton that there remains a problem to be solved. There is no explicit or implicit teaching, suggestion, or motivation to combine Benton, in view of Roninson, and further in view of Timberlake and further in view of Gossen.

The Patent Office cites Gossen for teaching, inter alia, the use of inducible promoters. However, Gossen makes no suggestion or motivation to modify or supplement the methods of Benton. Gossen makes no suggestion or motivation that there remains a problem to be solved in Benton. There is no explicit or implicit teaching, suggestion, or motivation in Gossen to combine the cited references, or, to modify Benton. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection under section 103 citing Benton, in view of Roninson, and further in view of Timberlake and Gossen, can be properly withdrawn.

Benton, in view of Roninson, and further in view of Timberlake and Mirabelli

Claims 25, 33 and 62 stand newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake and further in view of Mirabelli.

However, as discussed above, Applicants respectfully aver that there is no suggestion or motivation in the cited art, including Mirabelli, to modify or supplement Benton. There is no suggestion or motivation in Benton that there remains a problem to be solved. There is no explicit or implicit teaching, suggestion, or motivation to combine Benton, in view of Roninson, and further in view of Timberlake and further in view of Mirabelli.

The Patent Office cites Mirabelli, inter alia, for teaching screening randomly sheared antisense to identify new drugs and reagents for treatment. Mirabelli is cited for teaching "the cDNA can then be directionally cloned into the expression vector such that RNAs are produced in an antisense direction. This approach can identify new genes that are key to

successful infection." Mirabelli is discussing identifying genes that are key to successful infection.

However, Mirabelli makes no suggestion or motivation to modify or supplement Benton's methods for identifying essential genes. Mirabelli makes no suggestion or motivation that there remains a problem to be solved in Benton. There is no explicit or implicit teaching, suggestion, or motivation in Mirabelli to combine the cited references, or, to modify Benton. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection under section 103 citing Benton, in view of Roninson, and further in view of Timberlake and Mirabelli, can be properly withdrawn.

Benton, in view of Roninson, and further in view of Timberlake and Lam

Claims 72 to 74 stand newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake and further in view of Lam.

However, as discussed above, Applicants respectfully aver that there is no suggestion or motivation in the cited art, including Lam, to modify or supplement Benton. There is no suggestion or motivation in Benton that there remains a problem to be solved. There is no explicit or implicit teaching, suggestion, or motivation to combine Benton, in view of Roninson, and further in view of Timberlake and further in view of Lam.

The Patent Office cites Lam, inter alia, for teaching screening compounds including inorganic compounds, peptidomimetics, peptides or oligonucleotides.

However, Lam makes no suggestion or motivation to modify or supplement Benton's methods for identifying essential genes. Lam makes no suggestion or motivation that there remains a problem to be solved in Benton. There is no explicit or implicit teaching, suggestion, or motivation in Lam to combine the cited references, or, to modify Benton. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection under section 103 citing Benton, in view of Roninson, and further in view of Timberlake and Lam, can be properly withdrawn.

Benton, in view of Roninson, and further in view of Timberlake and Matsunaga

Claims 76 stands newly rejected under 35 USC §103(a) as allegedly unpatentable over Benton, in view of Roninson, and further in view of Timberlake and further in view of Matsunaga.

However, as discussed above, Applicants respectfully aver that there is no suggestion or motivation in the cited art, including Matsunaga, to modify or supplement Benton. There is no suggestion or motivation in Benton that there remains a problem to be solved. There is no explicit or implicit teaching, suggestion, or motivation to combine Benton, in view of Roninson, and further in view of Timberlake and further in view of Matsunaga.

The Patent Office notes that Benton, in view of Roninson, and further in view of Timberlake does not teach measurement of respiratory activity for cell viability. The Patent Office cites Matsunaga, inter alia, for curing this defect in Benton, in view of Roninson, and further in view of Timberlake.

However, Matsunaga makes no suggestion or motivation to modify or supplement Benton's methods for identifying essential genes. Matsunaga makes no suggestion or motivation that there remains a problem to be solved in Benton. There is no explicit or implicit teaching, suggestion, or motivation in Matsunaga to combine the cited references, or, to modify Benton. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection under section 103 citing Benton, in view of Roninson, and further in view of Timberlake and Matsunaga, can be properly withdrawn.

Evidence of secondary indicia of nonobviousness rebuts a prima facie case

Applicants submit herein sufficient evidence of secondary indicia of nonobviousness to rebut any possible *prima facie* case. By submission of the declarations of Dr. Gordon Foulkes and Dr. Robert Simons (first submitted in support of the parent application, USSN 08/971,090, now USPN 6,228,579), Applicants provide objective evidence of nonobviousness in that the instant claimed invention provided a long felt but unsolved need, there was an extreme skepticism by skilled artisans before the invention, that there were unexpected and surprising results created by the claimed invention, and that licenses showed

industry respect for the invention. Applicants respectfully aver that this objective evidence of nonobviousness is sufficient to rebut a possible *prima facie* case of obviousness.

Declaration of Dr. Gordon Foulkes

Dr. Gordon Foulkes, an expert in the fields of molecular biology and cell biology, declares that, in his opinion, there was a long-felt need in the biotech industry and the field of targeted drug discovery for an invention such as that set forth in the pending claims. Dr. Foulkes notes that major pharmaceutical companies had been employing a large amount of resources and a wide variety of different methods to identify new and effective targets for antibiotics. However, despite this recognized need and input of resources to identify methods for finding new antibiotic targets, and the availability of antisense methods over about the last 15 years, he is unaware of any company that successfully employed a method that could readily identify essential genes in pathogens until Elitra licensed and began practicing the novel, specific approach as set forth by the invention. In fact, initial attempts to apply this general approach by others met with little or no success.

Dr. Foulkes also relates how unexpectedly successful the invention has proven to be; practicing the methods of the invention has led to the identification of nearly 400 essential genes in the bacterium *Staphylococcus aureus* in less than 6 months. In total, over 700 essential genes have been identified in 5 bacterial species by using the methods of the invention. This success has been recognized by the invention's commercial success, as evidenced, for example, through licenses and collaborations showing industry respect for the invention. The interest by the drug industry to exploit the invention (by collaborating with Elitra, the exclusive licensee) has been and remains considerable. Dr. Foulkes concludes by declaring that this interest attests to the urgent need for new drug targets, the recognition of the success of the invention in finding new targets, and the limitations with existing methodologies.

Declaration of Dr. Robert W. Simons

Dr. Robert W. Simons, an expert in the general fields of molecular biology and molecular genetics, as well as the specific field of antisense RNA control, declares that, in his opinion, there is no express or implied suggestion in Escher to combine that teaching with Spann and that there is no express or implied teaching in Spann to combine that teaching with Escher.

Furthermore, Spann, using antisense cDNA, did not recognize that his method had deficiencies and did not suggest or recognize a need for an alternative source of nucleic acid to identify genes necessary in development. Dr. Simons declares that, in his opinion, the field of transcriptional activation (including transcriptional activator trap assays) and use of antisense cDNA to identify genes necessary in development (including assays for expressing different antisense cDNAs) are disparate arts. Dr. Simons declares that at the time of the invention, in 1997, based on either a general, fundamental understanding of these two disparate arts, or, based on a specific reading of Eschar or Spann, neither he, as an artisan skilled in these arts, nor another skilled artisan, would have been motivated to combine teachings from these two disparate arts, or, specifically, to combine Eschar and Spann.

Dr. Simons also declares that at the time of the invention, in 1997, he and his colleagues, skilled artisans in the field of artificial antisense RNA control, were skeptical that there was a way to readily identify artificial antisense sequences (in one embodiment, the invention readily identifies effective antisense sequences to identify microbial proliferation genes). Thus, such skepticism "taught away" from the use of antisense sequences to find a means to readily identify essential microbial proliferation genes. Dr. Simons also declares that at the time of the invention the extreme skepticism of the literature about the use of artificial antisense RNA control, in combination with the many published failed attempts at finding a general paradigm for identifying effective antisense, "taught away" from the idea that genes necessary for proliferation could be readily identified, particularly by use of artificial antisense RNA control. Dr. Simons concludes by opining that the numerous failures of diverse antisense RNA strategies, as reflected in the prior art as of 1997, rather than motivating the sort of innovative combination of elements that constitutes the instant invention, actually dissuaded and taught away from such innovation.

Dr. Simons also declares that when he and his colleagues first learned of the success of the methods of the invention they were amazed at the novelty of the invention and that it was possible to find a new antisense approach that worked so much better than existing methodologies to identify essential gene drug targets. Dr. Simons also notes that it has been appreciated that a major factor in the success of the invention was the use of large random libraries to generate those rare nucleotide fragments which, when expressed, possess functional

antisense (i.e., message inhibitory) properties. The success of the claimed method (in contrast to failures of the prior art) is due, in part, to use of large libraries of random genomic nucleic acid fragments, in which (surprisingly) there is almost always a fragment that will be inhibitory.

In view of the above remarks and the evidence of secondary indicia of nonobviousness as set forth in the declarations of Drs. Foulkes and Simons, Applicants submit that they have rebutted any possible *prima facie* case of nonobviousness. Accordingly, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. §103(a).

In view of the above remarks, Applicants respectfully submit that the pending claimed invention is not obvious over the cited art. Accordingly, the rejection under 35 U.S.C. §103(a) can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §103(a). Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If necessary, please apply additional and necessary charges, and apply all credits, to Deposit Account No. 06-1050.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: Oct. 06, 2003

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